Impact of Hepatitis C treatment on behavioural change in relation to drug use in people who inject drugs

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Title: Impact of Hepatitis C treatment on behavioural change in relation to drug use in people who inject drugs: a systematic review

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Title: Impact of Hepatitis C treatment on behavioural change in relation to drug use in people who inject drugs: a systematic review

Abstract

Background: A systematic review was conducted to determine the impact of Hepatitis C (HCV) treatment on substance use behaviour in people who inject drugs (PWID).

Methods: A search for peer reviewed journal articles from 1991 to present day was conducted using the following databases: PubMed, EMBASE, CINAHL and PsycINFO. Studies were appraised against the following inclusion criteria: recruitment of PWID for HCV treatment (either interferon alpha or direct acting antivirals based); measurement of behavioural change in relation to drug use; studies published in English.

Results: Five studies investigating the impact of HCV treatment on behavioural change in relation to drug use amongst PWID were identified. Studies investigated the impact of HCV treatment on past month injecting drug use (four studies), injecting frequency (two studies), needle and syringe borrowing (two studies) and injecting equipment sharing (three studies). Three of the four studies assessing impact of treatment on past month injecting frequency found treatment significantly reduced the odds of participants reporting past month injecting at follow up. One study found that there was significant reduction in weekly injecting frequency between enrolment, treatment and follow up. No association was found between treatment engagement and needle and syringe borrowing. Two out of three studies reported a significant decrease in injecting equipment sharing between enrolment, treatment and follow up.

Conclusions: Comparison and synthesis of results was challenging due to heterogeneity between studies. Moreover, four out of the five selected studies were conducted during the interferon era of treatment, possibly limiting the generalisability of the current review's results to the new DAA treatment era. However, it is likely that engaging in treatment has a positive

impact upon patients' injecting drug use and injection equipment sharing behaviour. This raises the possibility that this may be an opportune time for further harm reduction measures.

Keywords

Hepatitis C; People who inject drugs; Injecting risk behaviours; Behaviour change; Systematic review

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Introduction

Hepatitis C (HCV) is a blood borne virus which affects around 71 million people globally (World Health Organisation, 2017; Blach et al., 2017). It is estimated that 39.2% of PWID are currently living with HCV infection worldwide (Grebely et al., 2019). HCV infection is a major contributor to morbidity and mortality among this population (Stanaway et al., 2016). Research has supported the treatment of active drug users for Hepatitis C, demonstrating successful adherence to treatment and favourable sustained viral response rates (Hajarizadeh et al., 2018). This highlights the feasibility and effectiveness of scaling up treatment services to reduce the prevalence of the disease, using “treatment as prevention” (TasP) models of elimination (E. J. Aspinall et al., 2013; Fraser et al., 2018). TasP models of elimination focus on treating PWID for HCV as they are the most at- risk population for acquiring the virus. Therefore, HCV elimination can be achieved by treating those at risk of continuous HCV transmission (Hellard, Doyle, Sacks- Davis, Thompson, & McBryde, 2014; Hellard et al., 2015; Hutchinson et al., 2015). However, testing, diagnosis and treatment rates of HCV infection among PWID have found to be inadequate in some settings, despite evidence that the incidence of HCV- related liver disease is on the rise (Socías et al., 2019; Thrift, El-Serag, & Kanwal, 2017; Wiessing et al., 2014). Barriers to testing and treatment are complex, but include concerns among providers around ongoing risk behaviour, such as ongoing substance misuse, and the sharing of injecting paraphernalia; risk of reinfection; the worsening of psychiatric comorbidities; and poor treatment adherence (Grebely & Tyndall, 2011).

In spite of these barriers to treatment, there is a suggestion that the benefits of engaging with HCV care stretch beyond liver morbidity outcomes. Studies report the positive impact of HCV status notification on reduction in drug use among PWID (E. Aspinall et al., 2014; Bruneau et al., 2013). PWID accessing HCV treatment have the opportunity to develop a therapeutic

relationship with healthcare professionals involved in their care, which may facilitate behavioural change (Spelman et al., 2015).

Understanding the influence of treatment receipt on behaviour in relation to drug use in PWID may have an effect on treatment accessibility for this population, and may facilitate the development of supplementary support services to be offered with treatment. The objective of this review was to examine the literature investigating how, if at all, the behaviour of PWID changes in relation to drug use when undergoing HCV treatment and during follow up, including changes in injecting behaviour, injecting frequency, needle and/or syringe borrowing, and injecting equipment sharing.

Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). The study was registered in PROSPERO (CRD42018116625).

Search Strategy

The International Prospective Register of Systematic Reviews (PROSPERO) was searched to confirm no similar review had already been conducted. A search for peer reviewed journal articles was conducted using PubMed, EMBASE, CINAHL and PsycINFO, on 9th November 2018. A grey literature search of the International Network on Hepatitis in Substance Users (INHSU) conference abstracts was also conducted. This symposium was specifically targeted as it is dedicated to research focusing on Hepatitis C in the cohort of interest, namely PWID. A time parameter was implemented for studies conducted from 1991 to 2018, as 1991 was the year interferon became commercially available for treatment of Hepatitis C. An inclusive list of search terms in line with each search topic was generated to develop an effective search strategy. Both keywords and indexed subject headings (MeSH and EMTREE terms) were

included in the formulation of search strings for each database search. Search topics included “Hepatitis C treatment”, “behaviour change” and “drug use”. Table 1 includes a full list of search terms utilised in the search strategy, grouped by search topic. Manual searches of reference lists of selected studies were also conducted. Searches were limited to studies published in English.

Study selection

Fig. 1 shows a PRISMA flowchart of the selection process. Screening of the search strategy results was conducted by two reviewers. The first phase involved importing all citations into EndNote X8 and removing duplicate records. Titles were screened, and irrelevant records removed. Abstracts were then assessed using the inclusion and exclusion criteria (see Table 2). All remaining records were then subjected to a full text evaluation for eligibility.

Data Extraction and Synthesis

Data from selected studies was extracted using a piloted data extraction form by one reviewer (MC). The following variables were collected: first author, title, publication year, full paper or abstract, primary aim, study design, location, setting, total study duration, follow up period, sample characteristics, sample size, intervention, outcome/ measure of behaviour change, main results, conclusions. The authors of Malaguti et al. (2019) were contacted for clarification regarding follow up period in their study. The authors of Artenie et al. (2019) were contacted to obtain updated data, and they kindly provided an unpublished manuscript relating to their INHSU conference abstract. The data synthesis used a ESRC style quantitative narrative synthesis (Popay et al., 2006). This was used as there was too much heterogeneity between selected studies for meta- analysis.

Quality Appraisal

Risk of bias in individual studies was assessed using the Quality Appraisal Checklist for quantitative intervention studies by NICE public health guidance (National Institute for Health and Care Excellence, 2012). The checklist enables both the evaluation of the study's internal and external validity, addressing aspects of study design such as participant characteristics, definition of and allocation to intervention/control conditions, and methods of analyses. Each study was awarded separate overall quality ratings for internal and external validity, with ratings ranging from 1 to 3. Quality appraisal for four studies was independently conducted by two reviewers (MC and AM), with discrepancies in ratings resolved by discussion until consensus was met. A Cohen's kappa coefficient (κ) was calculated to assess inter-rater agreement, $\kappa = .61$, $p < .001$. This kappa (κ) value represents a substantial agreement (Landis & Koch, 1977). A third reviewer (ER), along with the first reviewer (MC), conducted a quality appraisal for the fifth study. This was necessary to reduce bias as the second reviewer (AM) was an author of the study. A Cohen's kappa coefficient (κ) was calculated to assess inter-rater agreement, $\kappa = .68$, $p < .001$, representing a substantial agreement (Landis & Koch, 1977).

Results

Search results

The database search produced a total number of 863 records. After removing duplicates (n= 141), a further 702 were removed after title and abstract screening. Twenty- one full text articles were assessed for eligibility, 16 were removed with reasons, leading to the final inclusion of 5 studies (see Fig. 1).

Characteristics of Selected Studies

Characteristics and findings of selected studies are summarised in Table 3. Studies evaluated impact of treatment on drug use by recruiting participants from a number of settings including tertiary hospitals; GP and primary care clinics; community clinics; drug and alcohol treatment

clinics; private medical practices; and injecting equipment provision services. There were four prospective cohort studies and one retrospective cohort study. Two studies included comparison groups in their study design. Alavi et al. (2015) utilised PWID that did not receive treatment as their comparison group. Artenie et al. (2017) utilised three comparisons groups, namely PWID who did not engage in treatment post- diagnosis; PWID who did not engage in treatment due to spontaneous clearance of the virus; and HCV positive PWID who were not eligible for treatment due to contra-indications.

Four studies investigated past month injecting drug use; two studies investigated injecting frequency; two studies investigated needle and syringe borrowing; and three studies investigated ancillary injecting equipment sharing. Of the five studies selected, four studies involved treatment with pegylated interferon alpha and/or ribavirin, with only one study involving treatment with direct acting antivirals (DAAs). Follow up periods ranged from 24 weeks to 2 years. In the sampled studies, the majority of participants were Caucasian males, with a mean age ranging from 32- 47 years old, who had injected drugs in the last 6 months prior to study enrolment. Two of the five selected studies solely recruited participants with acute HCV infection (Alavi et al., 2015; Artenie et al., 2017). Recruiting patients for treatment with acute HCV infection is not reflective of standard clinical practice, as these patients have a 20-30% of spontaneous clearance during the acute phase of the infection, making treatment uneconomical at this stage (Aisyah, Shallcross, Hully, O'Brien & Hayward, 2018). However, effect on injecting behaviour may still be relevant.

Risk of bias in individual studies

Table 4 provides detailed quality appraisal scores for each included study. The results of the scoring process suggests that Artenie et al. (2017) was the methodologically most robust study. Overall, the selected studies scored very highly on external validity. However, several issues of internal validity can be discussed. For instance, the occurrence of losses to follow up may have

caused selection bias in several studies, with sizeable differences in socio-demographic characteristics between participants who remained, versus lost to follow up. For example, Midgard et al. (2017) found that participants who remained in 12 weeks follow up were more likely to be employed, have higher education levels, had less history of incarceration, and had injected more often in the last month, in comparison to those lost to follow up. Therefore, it is possible that those remaining in follow up were more likely, for instance, to have greater access to social support, impacting on their ability to engage in treatment and facilitate behavioural changes in relation to their drug use. Another issue of internal validity is the lack of comparison groups in some studies, e.g. Artenie et al. (2019) and Midgard et al. (2017), making it challenging to attribute behavioural changes to the intervention, i.e. HCV treatment. A final point to note is the quality assessment tool's appraisal of the outcome variable's reliability. According to the Quality Appraisal Checklist's guidelines, outcome variables that are measured subjectively, e.g. self report, are to be scored poorly and could introduce information bias (National Institute for Health and Care Excellence, 2012). As all selected studies utilised a self-reported measure of injecting risk behaviours, they were all poorly scored for this part of the appraisal process. However, research has demonstrated that self-reported drug use among PWID is reliable and valid (Darke, 1998). Therefore, it is the opinion of the authors that the selected studies rate more highly for study design appraisal.

Results of individual studies

Impact of treatment on past month injecting drug use

Four studies investigated the impact of treatment on past month injecting drug use at various time points during treatment and follow up, assessed dichotomously (Alavi et al., 2015; Artenie et al., 2017; Artenie et al., 2019; Midgard et al., 2017). Alavi et al. (2015) reported no association between HCV treatment and past month drug use during 24 weeks follow up, when comparing PWID who did and did not receive treatment (aOR 1.06, 95% CI 0.93- 1.21, n= 124). However, this study did not differentiate between participants based on their reasons for not engaging in treatment after study enrolment, possibly explaining the non-significant results of the study as untreated participants are arguably a more heterogeneous cohort. A second study by Artenie et al. (2017) did make this distinction, evaluating the impact of treatment on injecting drug use at one year follow up when comparing people who received treatment, and three comparison groups: people who spontaneously cleared the virus and did not require treatment; people who were not eligible for treatment due to contra-indications to therapy; and people who voluntarily chose not to engage in HCV care. Results showed that the received treatment group were less likely to report drug use at follow up in comparison to the voluntary non- engagement group (aOR 0.18, 95% CI 0.04- 0.76, n=87). The odds of reporting drug use at follow up amongst the spontaneous clearance (aOR 0.34, 95% CI 0.08–1.40, n=87) and contra-indications to therapy groups (aOR 0.24, 95% CI 0.05– 1.22, n= 87), were not significantly lower in comparison to the voluntary non- engagement group. This finding is supported by Midgard et al. (2017) who found that there was a significant reduction in any past month injecting drug use during treatment and 12 week follow up (OR 0.89, 95% CI 0.83– 0.95, n= 93), with the likelihood of injecting halved at treatment completion compared to study enrolment. A fourth study evaluated the impact of DAA based treatment on past month injecting drug use and found that there was an overall significant reduction in opioid injecting (OR: 0.95, 95% CI 0.92- 0.99, n=

190) between treatment initiation and 2 year follow up (Artenie et al., 2019). However, no reduction in stimulant (cocaine and amphetamine) injecting was reported (OR 0.98, 95% CI 0.94-1.02, n=190).

Impact of treatment on injecting frequency

Two studies investigated the impact of treatment on injecting frequency. Midgard et al. (2017) measured ≥ daily injecting as a proxy for past month injecting frequency, and found that the proportion of participants who reported ≥ daily injecting did not significantly change during treatment and follow up (OR 0.98, 95% CI 0.89- 1.07, n= 93). It is notable that injection risk behaviours amongst participants in this study were low at baseline, with only 28% of participants who achieved 12 weeks follow up reporting ≥ daily injecting at enrolment. Moreover, the authors mention a lack of statistical power due to the relatively small sample size, providing a second explanation of lack of significant findings. A second study by Malaguti et al. (2019) investigated changes in weekly injecting frequency between enrolment, during treatment and at 6 months follow up. Results showed a significant decrease in injecting frequency between enrolment and future time points (χ^2 (7) = 36.44, p< .001, n= 32), with the largest reduction in injecting reported between enrolment and week 8 of treatment, maintained through to 6 months follow up. A criticism of this study may be the high degree of incomplete data, with only 38% of participants providing data for all time points.

Impact of treatment on needle and syringe borrowing

The impact of treatment on needle and syringe borrowing was investigated by two studies. One such study by Alavi et al. (2015) found that treatment was not associated with a reduction in needle and syringe borrowing during follow up, when comparing PWID who did and did not receive treatment (aOR 0.99, 95% CI 0.89, 1.07, n= 124). A second study found that treatment

receipt did not significantly facilitate a reduction in use of non-sterile needles (OR 0.94; 95% CI 0.79–1.12, n= 93) (Midgard et al., 2017).

Impact of treatment on injecting equipment sharing

Facilitation of a reduction in injecting equipment sharing by treatment was explored in three studies. One study reported a significant decrease in injecting equipment sharing, including mixing container, filter and water, during treatment and 24 weeks follow up (aOR 0.85, 95% CI 0.74- 0.99, n=124), with a reduction in the number of participants reporting sharing from 54% at baseline to 17% at follow up (Alavi et al., 2015). In contrast Midgard et al. (2017) reported no association between treatment and injecting equipment sharing, including spoons, mixing containers, drug solution, water and filter, during treatment and 12 week follow up (OR 0.87, 95% CI 0.70–1.07, n= 93). One study investigating the impact of DAA based treatment on behavioural outcomes reported a significant reduction in the number of participants reporting needle and syringe sharing during treatment and 2 year follow up (OR 0.87, 95% CI 0.80- 0.94, n= 190) (Artenie et al., 2019). However, it must be noted that although a reduction in needle and syringe sharing during and after treatment was noted, the baseline prevalence of this risk behaviour was low at only 16% of the 62% of participants who reported past month injecting.

Discussion

Summary of evidence

In spite of the concerns around diagnosing and treating PWID for Hepatitis C, there is a dearth of research on the impact of engaging in treatment on behavioural change in relation to drug use in this population. The current review only identified five studies which directly measured behavioural change outcomes in PWID engaged in treatment. As a consequence of the limited number of studies identified, and variations in follow up times, behavioural outcomes, and

treatment interventions, drawing conclusions around whether treatment engagement is effective in reducing drug use and injecting risk behaviours is problematic.

The most common outcome measure of behaviour change in relation to drug use in the selected studies was past month injecting drug use. Three of the four studies assessing this outcome found treatment significantly reduced the odds of participants reporting past month injecting at follow up (Artenie et al., 2017; Artenie et al., 2019; Midgard et al., 2017). However, due to variations in study design, comparing the findings of these separate studies is challenging. Accordingly, combining the data on these results to conduct a meta- analysis was deemed inappropriate. Additionally, it can be argued that dichotomously measuring past month injecting drug use is limiting in regards to providing insight into the impact of treatment on injecting behaviours. Combined with infrequent measurements of drug use, it could be suggested that the results of these studies simply reflect natural fluctuations in injecting frequency among PWID, and do not accurately reflect a reduction in drug use. However, taken together, these findings suggest that engaging in treatment may result in a possible reduction in injecting. This challenges critics who believe that treating PWID for Hepatitis C is not feasible due to concerns around treatment causing an increase in injecting risk behaviours (Schaefer, Sarker, & Diez-Quevedo, 2013). Moreover, these findings support the notion that treatment engagement may lower the risk of HCV transmission within the PWID population, providing support for accessibility to treatment.

In regards to impact of treatment on other behavioural changes related to drug use, findings are more inconsistent. For instance, of the two studies which investigated the impact of treatment on injecting frequency, only one study observed a significant decline in injecting frequency between enrolment, treatment, and follow up (Malaguti et al., 2019). Nonetheless, comparing the findings of these studies is not suitable due to the contrasting measurements of injecting

frequency; namely weekly injecting, measured as a continuous variable (Malaguti et al., 2019), and ≥ daily injecting, measured as a binary variable (Midgard et al., 2017).

Both studies investigating change in needle and syringe borrowing found no association between treatment engagement and reduction in these risk behaviours (Alavi et al., 2015; Midgard et al., 2017). Although no significant decline was observed in either study, the fact that such risk behaviours remain stable throughout treatment and follow up has meaningful implications for risk of reinfection and onward transmission. The minimisation of injecting risk behaviours after treatment is critical to optimise patients' chances of achieving sustained viral responses and to reduce HCV prevalence at a population level (Hickman, De Angelis, Vickerman, Hutchinson, & Martin, 2015). Of the three studies investigating the impact of treatment on injecting equipment sharing, two studies reported significant decreases in such behaviour between enrolment, treatment and follow up. However, of these two studies, one study by Artenie et al. (2019) was conducted during the DAA era of treatment, making the findings of this study incomparable to the other studies investigating this behaviour change.

Limitations of review

The predominant limitation of the current review was the number of studies that met the inclusion criteria and the lack of comparability between studies. As a consequence, a meta-analysis of findings was not possible. Therefore, future reviews may seek to employ a more broadly inclusive eligibility criterion, including, for example, the inclusion of purely qualitative studies. Moreover, it is clear that future research should focus on the reasons why engaging in treatment facilitates a possible behavioural change in relation to drug use. A major limitation of the review was that four of the five selected studies were conducted during the interferon era of treatment. In particular, the characteristics of people undergoing interferon treatment may potentially be different to those undergoing DAA treatment. For example, those treated using interferon based therapy may have experienced more adverse treatment consequences, such

as associated psychiatric conditions, in comparison to those treated using the DAA based therapy. Moreover, the reasons why engaging in treatment facilitates a positive behaviour change in relation to drug may be disparate between the aforementioned treatment groups. Consequently, the results of the current review may not give insight into the impact of treatment on injecting risk behaviours in the new DAA based treatment era, with future research clearly needed to clarify this issue. Also, the review was hindered by the inclusion of studies with selection bias of participants. All five studies involved clinical trial participants, who were arguably more willing to engage in treatment than the source PWID population. This was characterised by relatively low lost to follow rates in some studies. Thus, the results of the included studies may not be representative of the wider population of PWID engaging in treatment.

Conclusions

Five studies investigating the impact of HCV treatment on behavioural change in relation to drug use amongst PWID were identified. The most common measure of behaviour change in relation to drug use was past month injecting drug use, with three out of four studies reporting treatment significantly reduced the odds of participants reporting past month injecting at follow up. Studies also reported significant reductions in injection equipment sharing between enrolment, treatment and follow up; no significant changes in needle and syringe borrowing; and varying results in regards to impact of treatment on injecting frequency. Comparison and synthesis of results was challenging due to heterogeneity of follow up times, treatment interventions, and measures of behavioural outcomes. For future research, it would be optimal for the research community to report injecting risk behaviour in a standardised manner to enable comparison and strengthen conclusions of published literature. Four out of the five selected studies were conducted during the interferon era of treatment, possibly limiting the generalisability of the current review's results to the new DAA treatment era. However, results suggest the benefits of engaging in

HCV care stretch beyond liver morbidity outcomes, with treatment positively impacting on patients' injecting drug use and injection equipment sharing behaviour. These findings have relevance to the "treatment as prevention" model of Hepatitis C care, risk of reinfection and onward HCV transmission (Schulkind et al., 2018; Fraser et al., 2018).

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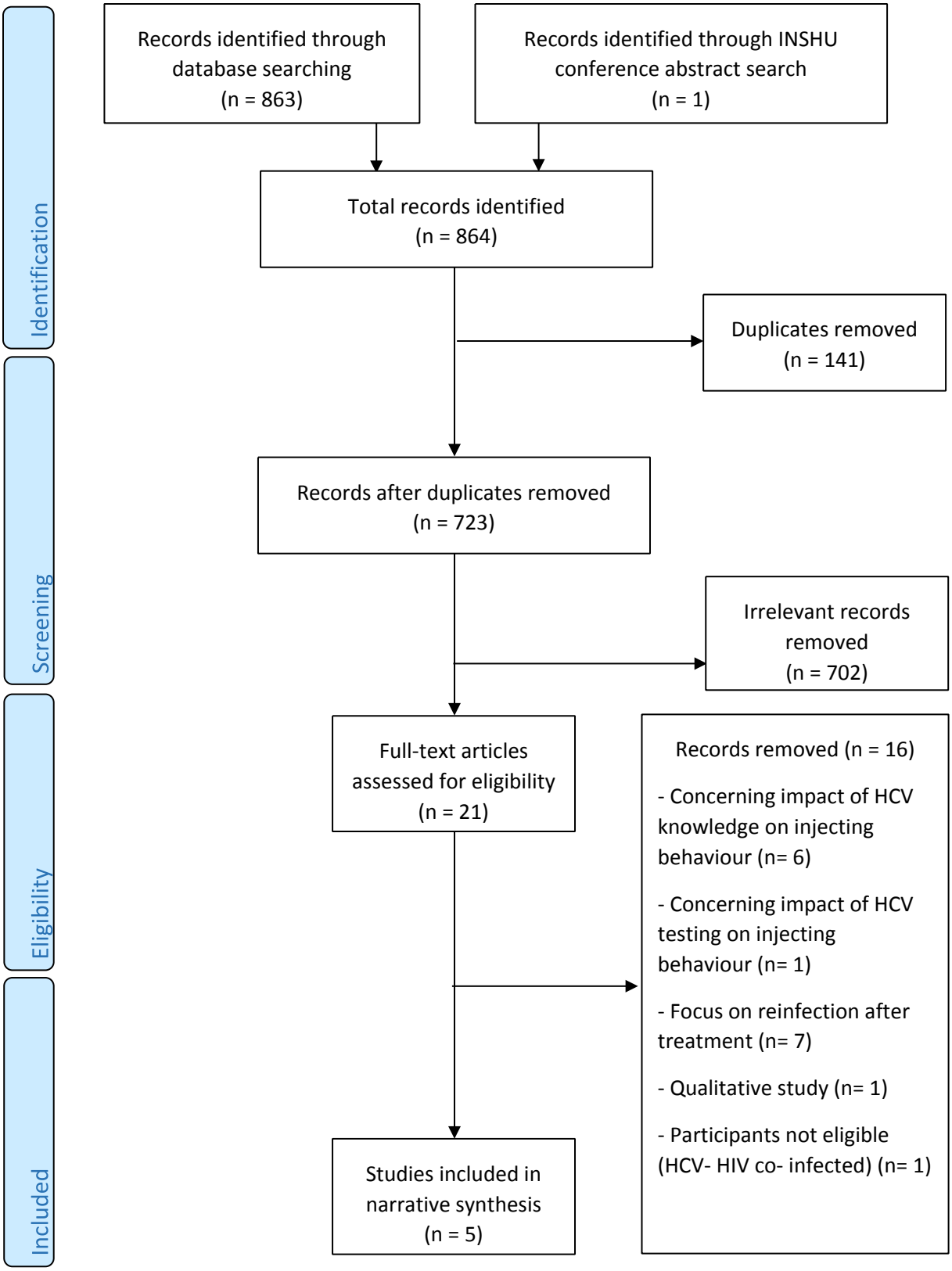

Figure 1. Search Strategy

Table 1

Keyword search terms utilised in search strategy, grouped by search topic

Hepatitis C treatment	Behaviour change	Drug use
Hepatitis C treatment/therapy^	Behavi* change	Drug abuse
Interferon-alpha/ therapeutic use^	Behavi* benefit	Drug misuse
	Drug use change*	Drug use
	Inject behavi*	Drug disorder
	Risk behavi*	Drug addict*
	Inject* frequency	Drug dependen*
		Drug intravenous*

^MeSH/EMTREE terms

Table 2

Inclusion/Exclusion Criteria

Inclusion Criteria
• Participants: people who inject drugs (PWID). • Study intervention: Hepatitis C diagnosis and treatment (either interferon alpha or direct acting antivirals based). • Comparators: participants themselves i.e. behaviour measured before and after treatment; or PWID who did not receive treatment; or PWID who chose to not engage in treatment post HCV diagnosis. • Primary outcome: behavioural change in relation to drug use e.g. injecting behaviour, needle and syringe borrowing, sharing of ancillary equipment. • Studies published in English, utilising a quantitative or mixed- methods study design.
Exclusion Criteria
• Studies utilising a purely qualitative study design; individual case studies. • Studies that are entirely theoretical. • Participants who are non- injecting patients, or PWID who were treated for other blood borne viruses. • Studies investigating the impact of Hepatitis C treatment in prison populations. • Studies focusing on the impact of knowledge of HCV status, and not HCV treatment, on behavioural change in relation to drug use. • Studies focusing on reinfection rates after treatment.

Table 3

Summary of Study Characteristics

Study *Country*	Measure of behaviour change	Design (comparison group(s)) *Follow up period*	Setting	Participant characteristics- age, gender, past month injecting drug use, on OST, HCV status	Treatment	Main Findings
Alavi et al. (2015) *Australia*	Past month Injecting drug use, used needle and syringe borrowing and ancillary injecting equipment sharing at baseline, throughout and after treatment	Prospective cohort study (PWID that did not receive treatment) *24 weeks*	Tertiary hospitals and GP/primary care clinics	124 participants, Mean age= 32 years (25- 39 years), 69% male, past month injecting drug use= 45%, on OST= 18%, recent HCV infection.	Pegylated interferon alpha and ribavirin treatment (up to 24 weeks)	Injecting drug use during follow up was not associated with treatment. Needle and syringe borrowing during follow up was not associated with treatment. Treatment associated with a reduction in ancillary injecting equipment sharing during follow up.

Artenie et al. (2017) *Canada*	Past month injection drug use assessed dichotomously at 12 month treatment follow up	Prospective cohort study (PWID who did not engage in treatment post-diagnosis; did not engage due to spontaneous clearance; not eligible for treatment due to contra-indications) *1 year*	Community and hospital based clinics	87 participants, Mean age= 35.6 years, 78% male, past month injecting drug use= 87.4%, on OST= 37.9%, acute HCV infection.	Pegylated interferon alpha and ribavirin treatment (up to 24 weeks)	Participants who received treatment were significantly less likely to report injection drug use at one-year follow-up compared to comparison groups.
Artenie et al. (2019) *Australia, Canada, New Zealand, Norway, Switzerland, France, UK and USA*	Past month injection drug use, needle/ syringe sharing, hazardous alcohol use during and following treatment	Prospective cohort study (none) *2 years*	Drug treatment clinics, hospital clinics, private practice, community clinics	190 participants, Mean age= 47 years, 74% male, past month injecting drug use= 62%, on OST= 61%, active HCV infection.	Direct acting antivirals (12 weeks)	Overall decrease in opioid injecting during and following treatment. No changes found in hazardous alcohol consumption observed. Decrease in needle and syringe sharing during and following treatment.

Malaguti et al. (2019) *United Kingdom*	Injecting frequency at baseline, throughout and after treatment	Retrospective cohort study (none) *6 months*	Injecting Equipment Provision (IEP) Service	84 participants (18 to 70 years), 69% male, past month injecting drug use= 100%, on OST= 71.4%, active HCV infection.	Pegylated interferon alpha and ribavirin treatment (up to 24 weeks)	Significant reduction in injecting frequency between baseline and subsequent future time points. Largest reduction between week 1 (baseline) and week 8.
Midgard et al. (2017) *Australia, Canada, Switzerland, Belgium, Germany, Norway and the UK*	Past month injection frequency, use of non-sterile needles, needle and syringe borrowing or lending, and injecting paraphernalia during and following treatment	Prospective cohort study (none) *24 weeks*	Hospital clinics, drug and alcohol clinics, office based practices and community clinics	93 participants, Median age= 41 years (35- 50 years), 83% male, past month injecting drug use= 59%, on OST= 71%, chronic HCV infection.	Pegylated interferon alpha and ribavirin treatment (up to 24 weeks)	Injecting drug use decreased during treatment and follow-up. No significant changes were found in >daily injecting, use of non-sterile needles, sharing of injecting paraphernalia, or non-injecting drug use.

Table 4

Quality appraisal ratings for each included study

	Alavi et al. (2015)	Artenie et al. (2017)	Malaguti et al. (2019)	Midgard et al. (2017)	Artenie et al. (2019)
1.1 Description of source population	3	3	3	3	1
1.2 Representativeness of eligible population	3	3	3	3	2
1.3 Representativeness of selected participants	2	3	2	2	2
2.1 Allocation to intervention or comparison	NA	NA	NA	NA	NA
2.2 Description of intervention and comparison	3	3	2	3	2
2.3 Concealment of allocation	NA	NA	NA	NA	NA
2.4 Blinding to exposure/comparison	NA	NA	NA	NA	NA
2.5 Adequacy of exposure to intervention/comparison	NA	NA	NA	NA	NA
2.6 Contamination	NA	NA	NA	NA	NA
2.7 Similarity of other interventions to groups	3	3	NA	NA	NA
2.8 Lost to follow up	1	2	2	2	1
2.9 Setting reflects usual UK practice	2	2	3	3	2
2.10 Intervention reflects usual UK practice	2	2	3	3	2
3.1 Reliability of outcome measures	1	1	1	1	1
3.2 Completion of outcome measures	3	3	3	3	3

3.3 Assessment of important outcomes	NA	NA	NA	NA	NA
3.4 Relevance of outcomes	3	3	3	3	3
3.5 Similarity of follow up times across groups	NA	NA	NA	NA	NA
3.6 Meaningfulness of follow up times	3	3	3	3	3
4.1 Similarity of groups at baseline	3	3	NA	NA	NA
4.2 Intention to treat (ITT) analysis	NA	NA	NA	NA	NA
4.3 Study's power to detect an intervention effect	2	2	2	2	2
4.4 Estimates of effect size	3	3	3	3	3
4.5 Appropriateness of analytical methods	3	3	3	3	2
4.6 Precision of intervention effects	3	3	3	3	3
5.1 Internal validity	2	3	2	2	2
5.2 External validity	3	3	3	3	3